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Pre–Hospitalization Care Settings and hyperglycaemic Emergencies in a Tertiary Hospital, South East Nigeria

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Abstract
Background: *Hyperglycaemic emergency (HE) is a frequent complication of diabetes mellitus (DM) and one of the commonest causes of hospitalization and death among people living with diabetes and previously unknown diabetes. Mortality from HE is still high in developing countries such as Nigeria; mortality being dependent on co-morbid conditions and precipitating factors. There is a paucity of published reports in the literature of any association between pre-hospitalization care settings and outcome of HE treatment, hence, the need for this study.*
Materials and Methods: *This was a prospective observational study carried out to assess the association between pre-hospitalization care settings (see definition of terms) and outcome of HE managed at Federal Medical Centre (FMC) Umuahia, Nigeria. One hundred and ten consecutive adult patients managed for HE at FMC, Umuahia were studied. Data from the subjects included bio-data, history of being a known diabetic or not, where diabetes care was accessed and anti-diabetic medications prior to HE. Primary outcome measures were survival and death. Analysis of data was done using SPSS 20.0 and the level of statistical significance was set at $p < 0.05$.*
Results: *Mean age of subjects was 58.10 ± 15.03 years. Male: female ratio was 1: 1.4.While HE constituted 15.6% of all medical admissions, mortality from HE was 10%. Most of the new onset diabetes and all the fourteen subjects who were accessing diabetes care from the diabetes clinic of FMC, Umuahia or similar tertiary health facilities survived. Forty five (90%) of the 50 subjects who were accessing care at the peripheral hospitals survived. A significant association was found between pre-hospitalization care settings and outcome of HE.*
Conclusion: *This study has shown that the pre-hospitalization care setting of patients managed for HE has a significant contribution to the outcome of treatment. It, also, showed that new-onset diabetes is not associated with poor outcome.*
Keywords: *pre-hospitalization care settings, HE, new-onset diabetes, outcome of hospitalization.*

Introduction

Hyperglycemic emergency is one of the acute complications of DM and it refers to potentially fatal acute metabolic complications of DM typically represented by diabetic ketoacidosis, (DKA) and hyperosmolar hyperglycemic state, (HHS)[1]. Globally, mortality rate of HHS ranges from 10 – 50% which is considerably higher than that of DKA[2, 3] which is 1.2 – 9%.

Prevalence of hyperglycemic emergency in Nigeria is unknown[4] but it is a major cause of diabetic deaths. Hyperglycemic emergency was the diagnosis in many Nigerians (55.2%) who were not previously diagnosed as having diabetes[5].

It is a major cause of hospital admissions for diabetic patients[6] in Nigeria and factors responsible for the high mortality associated with hyperglycemic emergency in Nigeria[7] include inefficient health system, inadequate diabetes care facilities, poor laboratory support, lack of qualified health personnel, ignorance of those living with diabetes about the acute complications of diabetes, poverty of the patients and their caregivers who pay for the services rendered from their pockets.

Prognosis of DKA and HHS is worsened with increasing age, presence of coma and hypotension[8, 9]. Death in cases of hyperglycemic emergency is rarely due to metabolic complications of hyperglycemia or ketoacidosis but often from the underlying precipitating illnesses[10] Mortality was usually due to precipitating causes, electrolyte imbalance especially hypo- and hyperkalemia and cerebral oedema[11].

There has, however, been no published reports in the literature of association between the pre-hospitalization care settings and the outcome (survival, death and hospitalization duration) of HE. This study, therefore, set out to determine the influence of pre-hospitalization care settings to the outcome of patients managed for HE in Federal Medical Centre. (FMC) Umuahia, South East, Nigeria.

Materials and Methods

Study design and site

This was a prospective observational study conducted at the Accident and Emergency (A & E) department and medical wards of Federal Medical Centre, Umuahia in Abia state, South East, Nigeria. Umuahia is a metropolitan town with some commercial activities going on in the city. Some study subjects were recruited when they sought treatment at the diabetes and medical outpatient clinics. Each recruited subject was admitted, appropriate treatment commenced and outcome of treatment in the Emergency room and medical wards (well and discharged home, discharged against medical advice or died) were recorded. From the emergency room and in the medical wards, such patients with a diagnosis of hyperglycaemic emergency (DKA, HHS etc) were managed using the local treatment protocol of the Department of Internal Medicine, FMC, Umuahia (Appendix 1). Ethical approval for the study was obtained from the Health Research Ethics Committee of FMC, Umuahia and the recruited patients gave informed consent when they recovered consciousness or became more clinically stable.

Sample size and sampling

The sample size was calculated using appropriate formula[12] based on incidence rate of hyperglycaemic emergencies (DKA and HHS) of 12% recorded in Iddo Ekiti[13]. Participants who consented to the study were consecutively recruited.

Inclusion and exclusion criteria

Persons living with diabetes and new onset diabetes aged 18 years and above with a diagnosis of hyperglycaemic emergency (see definitions of operational terms below) admitted via the Accident and Emergency unit, diabetes clinic or medical outpatient clinic were included in the study. Patients diagnosed with hyperglycaemic emergencies which started while in the intensive

care unit (ICU), surgical, medical and obstetric/ gynaecological wards were also recruited. However, patients who declined consent when they became stable/conscious and those who had co-existing congestive heart failure, end-stage renal disease or other major organ failures were excluded from the study.

Recruitment and Data Collection

From July 2015 to March 2016, using the consecutive type of non-probability sampling technique[14], the participants were recruited. Of the 123 accessible subjects that met the diagnostic criteria for hyperglycaemic emergency on presentation at FMC, Umuahia, 5 died few hours after admission in A & E before being investigated, 3 were less than 18 years, 5 refused to give informed consent when they recovered consciousness and 110 subjects were recruited, having met the inclusion criteria.

Data for the study was obtained from two sources thus:

1. Data extracted from ward admission/discharge register, death certificates and follow up of each of the subjects as they were being treated for HE from admission till they left the hospital which included total number of medical and diabetic admissions within the study period and the outcome of admission (survived, discharged home against medical advice or died).
2. Data extracted from researcher - adminstered questionaires which included socio-demographic data, history of being a known diabetic or not, where diabetes care was accessed and anti-diabetic medications prior to HE.

Each participant, at presentation and while on admission, had the following physical examination findings noted: temperature, level of dehydration, level of consciousness, pulse rate and respiratory rate. Each participant's blood pressure (BP) was measured using a mercury sphygmomanometer (Accoson, England) at heart level using appropriate cuff size.

The understated laboratory tests were done to define DKA, HHS, HE etc.

Each subject's random plasma glucose was measured using the glucose oxidase method of Trinder[15], plasma electrolytes were measured using the method of ion-selective electrode[16] (ISE), plasma urea was measured using an enzymatic (urease) method while plasma creatinine was determined by the Jaffe's alkaline picrate kinetic method[17]. Plasma 3-beta hydroxybutyrate was measured for each subject using an enzymatic[18] (3-hydroxybutyrate dehydrogenase) oxidation of D-3-hydroxybutyrate to acetoacetate. Similarly, urine sample was collected from each subject for analysis. (glucose, protein and ketone) using Combi-10 strips.

Plasma osmolality was calculated using **2 x plasma sodium (mmol/L) + plasma glucose (mmol/L) + plasma urea (mmol/L)**

The outcome measures were patient's survival, hospitalization duration and death.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, USA) version 20.0 statistical software was used for data analysis. For continuous variables such as the ages and duration of hospital stay of the study subjects, mean values and standard deviations (SD) were calculated and the means compared using two sample t-test and ANOVA without posthoc test respectively. Categorical variables such as sex and outcome of HE were summarized using proportions expressed in percentages. The categorical variables were compared using the nonparametric test – chi squares. Fisher's exact test was not applied as the table was not a 2x2 contingency table. The level of statistical significance was set at $p < 0.05$.

Definitions of Operational Terms[3]

1. Type 1 DM patients were diabetic patients, typically diagnosed before age 30, who required insulin injection for survival from the time of diagnosis Type 1 DM could present at any age due to variability in the rate of beta cell destruction.

2. Type 2 DM patients were patients who were not dependent on insulin for survival from the time of diagnosis; such patients were surviving on diet, lifestyle modifications and glucose – lowering drugs but may require insulin for control of hyperglycaemia.
3. New onset diabetes were persons diagnosed with diabetes on the present admission.
4. Hyperglycaemic emergency– a medical emergency in which a person living with diabetes or new onset diabetes had symptoms of acute metabolic decompensations, was dehydrated (hypovolaemia), had random plasma glucose of ≥300mg/dl with or without impaired mental status[19, 20] and required immediate intravenous fluid and soluble insulin for resuscitation.
5. DKA was a biochemical diagnosis in which plasma glucose ≥300mg/dl, ketonuria ≥ 2+, normal plasma osmolality and HCO3 < 15 mmol/l.
6. HHS – also a biochemical diagnosis in which plasma glucose was ≥ 500mg/dl, plasma osmolality ≥ 320mosmol/kg, had absent or minimal ketonuria and plasma HCO3 > 15mmol/l and altered mental status due to hyperosmolality.
7. Normo-osmolar nonketotic hyperglycaemic state (NNKHS) – plasma glucose ≥ 300mg/dl, normal plasma osmolality 270 - 290mosmol/kg with nil or minimal ketonaemia/ketonuria
8. Mixed or indeterminate form – had features of DKA and HHS at the same time thus: HCO3 < 15mmol/l, plasma osmolality ≥ 320mosmol/kg with ketonuria ≥ 2+ or vice versa.
9. Pre-hospitalization care settings - referred to the type of health facility or hospital a person living with diabetes was accessing diabetes care prior to being admitted for HE irrespective of personnel that work there, treatment given or size of the outfit. The prehospitalizstion care settings included:
* tertiary hospitals such as FMC, umuahia,
*peripheral hospitals (see definition of term below),
*Paramedics such as neighborhood nurses, medical laboratory scientists/technicians, pharmacists and patent medicine dealers.
*new onset diabetes (defined above)
10. Peripheral hospitals - referred to all health facilities providing primary and secondary health services irrespective of size, type of personnel or medications given.

Results

Of the 705 patients admitted into the medical wards (male and female) via the medical outpatient clinics and Accident & Emergency unit of FMC, Umuahia within the 9-month study period of July 2015 to March 2016, 135 of them (19.15%) had diabetes mellitus-related complications. The 110 participants who met the inclusion criteria for this study constituted 15.6% of the total medical admissions and 81.5% of the diabetes mellitus-related complications within the period. Three of the subjects (2.7%) had type 1 diabetes mellitus while 97 (97.3%) had type 2 DM. A total of 46 males and 64 females participated in the study with a male – female ratio of 1:1.4; age range was 18 – 90 years, median age 56.50, mean age was 58.10 ± 15.03 years and the interquartile range was 25. There was no statistically significant difference between the mean age of male and female subjects (60.9 ± 15.1 versus 56.1 ± 14.8 respectively, t =1.692, p =0.73.

Prior to presentation with hyperglycemic emergency, diabetes status, care settings and medications were as shown in table 1 below.

Table 1: Pre-hospitalization status of the 110 subjects

Characteristics	Number	Percentage(%)
Diabetes status:		
Diagnosed Dm prior to HE	78	71
New-onset diabetes	32	29
Diabetes care prior to HE		
Diabetes clinic, FMC, Umuahia	14	12.8
Peripheral hospitals	50	45.5
Paramedics	14	12.8
None	32	29.1
Medications prior to HE		
Oral anti-diabetic drugs(OAD)	66	58.9
Insulin and OAD	9	8
Lifestyles(diet & exercise) only	35	31.3
Insulin alone	0	0

The range of duration of hospitalization of the subjects was 3 – 105 days with a mean duration of hospital stay at 18.96 ± 21.69 days, median duration 10.00 and interquartile range was 10. The mean duration of hospital stay for the females, 21.06 ± 23.86 was more than that of the males 16.04 ± 18.11. While 99 of the subjects (90%) were discharged home, 11 (10%) died (table 2)

Table 2: **O**utcome patterns of hyperglycemic emergency in FMC, Umuahia

Outcome	Frequency	Percentage	Mean duration of hospital stay(days)
Died	11	10.0	9
Dischargedhome	99	90	22.9
Total	110	100	

Of the 14 subjects who were accessing diabetes care from the diabetes clinic, FMC, Umuahia and similar health facilities, all were discharged home well. Only 2 of the 32 new-onset diabetes managed for HE died. The differences in outcome of hospitalization noted for the different pre-hospitalization care settings were statistically significant (X^2= 12.56, p= 0.006). New onset diabetes did not confer a statistically significant difference to outcome of HE managed at FMC, Umuahia.

Table 3: Relationship between pre-hospitalization care settings and outcome of HE in FMC, Umuahia

	survived	Died	Total
DM care prior to HE			
Diabetes clinic, FMC	14	0	14
Peripheral hospital	46	4	50
Paramedics	9	5	14
New onset diabetes	30	2	32

FMC = federal medical center, Umuahia. X^2 = 12.56, p = 0.006.

The mean duration of hospital stay for the different pre hospitalization care settings is shown in table 4 below. Analysis of variance (ANOVA) carried out to compare the mean duration of hospital stay for the 4 care settings did not show any significant differences and there was no need for posthoc test (f = 1.649, df =3, p = 0.183)

Table 4: Prehospitalization care settings and duration of hospitalization

Prehospitalization care settings	Mean duration of hospital stay(days)
1.FMC Umuahia and similar facilities	21.92
2. Peripheral hospitals	22.4
3. Paramedics (nurses, lab scientists, patent medicine dealers, pharmacy)	19.7
4. No previous DM care	12.0

Discussion

The main findings of this study were that HE constituted 15.6% of the total medical admissions within the study period, mortality from HE was 10%, pre-hospitalization care settings had significant association with HE outcome while new onset diabetes was not associated with adverse HE outcome.

This finding of HE accounting for 15.6% of all medical admissions was higher than the 3.6% reported by Okoro et al[21]. This could have been a result of increased health/diabetes awareness and increased diagnosis especially of new onset diabetes mellitus. The trend could also be in keeping with projected increasing prevalence of T2DM as a result of obesity, sedentary lifestyles, increased urbanization and westernization[22]. The contribution of HE to medical admissions (15.6%) in this study was similar to the 15% of all medical admissions reported by Ogbera et al in Lagos[4]

Death from HE (10%) in the index study was higher than the 4.8% and 3.57% reported from Benin[23, 5], 4.8% reported by MacIsaac et al[2] and similar rates in South Africans[24] This is probably due to late presentation to the Accident and Emergency department and death arising from the precipitating factors and other co-morbid conditions.

On the other hand, mortality rate in this study was lower than 18.8% and 16% reported by Adesina[25] and Ehusani[26] respectively, 18% by Ogbera et al[27], 27.7% by Eregie and Unadike[28] in Benin and 25 – 33% in some previous studies in East Africa[29, 30]. This could have been because of improved laboratory support services as important analytes such as plasma potassium, electrolytes, urea, creatinine and beta-hydroxybutyrate are now obtainable in shorter time than before and the diabetes care team was involved early in the management of most of these cases of HE.

In this study, there is a significant association between pre-hospitalization care settings and outcome of HE managed at FMC, Umuahia. That all the subjects accessing diabetes care at the diabetes clinic of FMC, Umuahia and similar health facilities had a favorable outcome (all survived) cannot easily be explained. However, it could be because monitoring and diabetes self management education (DSME) are implemented more strictly at the diabetes clinic manned by the diabetes care team than in the peripheral hospitals. Such patients are more likely to be on insulin or a combination of insulin and oral anti-diabetic drugs in a bid to achieve a good glycaemic control than patients accessing care at the peripheral hospitals and from other sources. The implication of the above findings is that all people living with diabetes should be under the care and supervision of a specialist in diabetes care.

It is important to point out that prehospitalization care settings contribute to theoutcome of HE in the presence of other prognostic factors such as age of patient, level of consciousness at presentation, electrolytes derangement, precipitating illnesses and co-morbid conditions. The study did not look whether it was an

independent predictor of death in HE.

Finally, that new onset diabetes did not have a significant association with adverse outcome of HE in the index study is at variance with the report by Ogbera et al[27] where previously undetected DM was predictive of fatal outcome from HE.

Conclusion/Recommendations

People living with diabetes accessing care at tertiary hospitals prior to having HE had a better outcome than others being followed up in peripherial centers before having similar complication of DM. Monitoring and diabetes self management education should be emphasized and implemented at all health facilities as is done in diabetes clinics of tertiary health institutions.

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APPENDIX 1:

SUMMARY OF DEPARTMENT OF INTERNAL MEDICINE, FEDERAL MEDICAL CENTRE, UMUAHIA, 'UMUAHIA PROTOCOL' FOR THE TREATMENT OF HYPERGLYCAEMIC EMERGENCIES

1) Patient is admitted at A & E or medical ward, specimen samples are collected for random plasma glucose, plasma electrolytes, urea creatinine and urine analysis for protein and ketone.
2) Fluid replacement with normal saline; rate of replacement being dependent on degree of dehydration, age and other associated factors.
3) Intravenous insulin administration; bolus dose stat and hourly doses till random plasma glucose is ≤ 250mg/dl.
4) Potassium replacement, dose being dependent on plasma potassium concentration which is monitored 2 hourly.
5) Empirical broad-spectrum antibiotics are used when infection is suspected as a precipitating factor.
6) Treatment of precipitating factors when identified.
7) Monitoring – hourly random blood glucose check initially, pulse, BP, respiratory rate and fluid input/output.
8) For HHS, prophylactic low dose Enoxaparin is given